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(54) Title: MR CONTRAST AGENT			
(57) Abstract <p>A composition for use as a contrast medium being particularly suitable for imaging of the stomach, liver, bile duct and gall bladder, said composition comprising as an active ingredient a physiologically acceptable manganese compound and an uptake promoter, wherein the uptake promoter comprises a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D.</p>			

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MR contrast agent

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The present invention relates to improvements on and  
5 relating to magnetic resonance imaging (MRI) and in particular to compositions for use as or in the preparation of MRI contrast media for imaging of the stomach, liver, bile duct and gall bladder. The MRI contrast media may also be used for imaging the pancreas and the heart.

10

MRI is now well established as a medical diagnostic tool. The ability of the technique to generate high quality images and to differentiate between soft tissues without requiring the patient to be exposed to ionizing radiation  
15 has contributed to this success.

Although MRI can be performed without using added contrast media, it has been found that substances which affect the nuclear spin reequilibration of the nuclei (hereinafter the  
20 "imaging nuclei" - generally water protons in body fluids and tissues) responsible for the magnetic resonance (MR) signals from which the images are generated may be used to enhance image contrast and, accordingly, in recent years, many such materials have been suggested as MRI contrast  
25 agents.

The enhanced contrast obtained with the use of contrast agents enables particular organs or tissues to be visualised more clearly by increasing or by decreasing the  
30 signal level of the particular organ or tissue relative to that of its surroundings. Contrast agents raising the signal level of the target site relative to that of its surroundings are termed "positive" contrast agents whilst those lowering the signal level relative to surroundings  
35 are termed "negative" contrast agents.

The majority of materials now being proposed as MRI contrast media achieve a contrast effect because they contain paramagnetic, superparamagnetic or ferromagnetic species.

5

For ferromagnetic and superparamagnetic contrast agents, which are negative MRI contrast agents, the enhanced image contrast derives primarily from the reduction in the spin reequilibration parameter known as arising from the effect 10 on the imaging nuclei of the fields generated by the ferromagnetic or superparamagnetic particles.

Paramagnetic contrast agents on the other hand may be either positive or negative MRI contrast agents. The effect 15 of paramagnetic substances on magnetic resonance signal intensities is dependent on many factors, the most important of which are the concentration of the paramagnetic substances at the imaged site, the nature of the paramagnetic substance itself, and the pulse sequence 20 and magnetic field strength used in the imaging routine.

Generally, however, paramagnetic contrast agents are positive MRI contrast agents at low concentrations where their  $T_1$  lowering effect dominates, and negative MRI 25 contrast agents at higher concentrations where their  $T_2$  lowering effect is dominant. In either event, the relaxation time reduction results from the effect on the imaging nuclei of the magnetic fields generated by the paramagnetic centres.

30

The use of paramagnetic, ferromagnetic and superparamagnetic materials as MRI contrast agents has been widely advocated, and broad ranges of suitable materials have been suggested in the literature.

35

An example of a physiologically acceptable paramagnetic material known for use as an MRI contrast agent is manganese ion, which may conveniently be used in the form of its salts, chelates or other complexes. Indeed, even at 5 very low intravenuos dosages (about 5-10  $\mu\text{mol}/\text{kg}$  body weight) manganese ions have been found to be particularly effective as a contrast agent for imaging of the liver.

However, manganese, when administered intravenously as a 10 contrast agent, may be teratogenic at clinical dosages. Administered intravenously, manganese is also known to interfere with the normal functioning of the heart by replacement of calcium in the calcium pump of the heart. It has been reported that dosages of manganese injected into 15 rats in excess of 0,1 mmol/kg body weight were often lethal.

In order to reduce the direct effect on the heart, oral administration has been proposed. This ensures passage of 20 the contrast agent through the liver before going to the heart and thereby decreasing the possibility of a heart attack.

Oral administration of  $\text{MnCl}_2$  as a liver imaging MR contrast 25 agent has been proposed, and orally administered  $\text{MnCl}_2$  has not been found to be teratogenic. However, the adsorption of  $\text{MnCl}_2$  through the gut is poor, and as a result the dosage required for clinical efficacy is of the order 100-1000  $\mu\text{mol}/\text{kg}$  body weight. In the event of damage to the gut 30 resulting in increased uptake, such a high dosage level still has the potential for causing undesired adverse effects, e.g. cardiac effects.

The toxicity of manganese ions precludes their 35 administration in amounts large enough to be useful in MRI.

It has been found that paramagnetic chelates are less toxic than the free ions, but the chelation will prevent or reduce the enhancement of binding of paramagnetics with tissues. This means that a greater amount of the chelate 5 will be needed to produce the same effect as the free ions.

EP A2 308 983 describes a MR imaging composition containing manganese(II) coordination compounds and their use in MRI. The invention is in particular directed to manganese(II) 10 coordination complexes with water-soluble amino acids, to MR imaging compositions containing these complexes, and to their use in MRI. These compounds have proven to be more safe and provide the same relaxivity as manganese salts. The non-chelated compounds do not affect the binding of 15 manganese to body tissue and blood components, and particularly heart and liver tissue, and reduce the toxicity. Solutions of the compound can be administered rectally, orally or parenterally, preferably parenterally.

20 Although it is stated that these solutions may be administered orally, none of the examples show what oral dosage is necessary to achieve a measurable MR image. Only injected dosages have been reported, and these dosages are not sufficient for oral administration.

25 We have now surprisingly found that gastrointestinal tract manganese contrast agents suitable for imaging of the liver may be produced by the incorporation of an uptake promoter capable of enhancing manganese transport across the 30 membranes of the gastrointestinal tract.

Compounds which have been found to be suitable for use as uptake promoters include amino acids, vitamin D or a combination thereof.

Thus, viewed from one aspect the present invention provides a contrast medium composition comprising a physiologically acceptable manganese compound, an uptake promoter and a physiologically acceptable carrier or excipient, wherein

5 the uptake promoter comprises an amino acid and/or vitamin D.

The contrast medium composition according to the invention may comprise a manganese compound together with a mixture

10 of several uptake promoters, i.e. a mixture of several amino acids and/or vitamin D.

The manganese compound, which preferably is soluble in gastrointestinal fluid, may for example be a salt, a

15 chelate or another complex, or may be a mixture of different salts, chelates and/or complexes. Particularly preferred are metal chelates and salts in which the manganese is present as Mn(II) rather than Mn(III), since the former has a higher magnetic moment and thus is more

20 effective as a MR contrast agent. Suitable salts are salts of inorganic anions, e.g. chlorides, bromides, iodides, flourides, sulfates, phosphates, preferably chlorides and salts of organic anions.

25 Another manganese source is manganese containing foodstuff such as blueberry juice, green tea and nuts. Also these manganese sources may be combined with an uptake promoter according to the invention.

30 The reducing nature of the uptake promoter is important since normal uptake of manganese by the gut tends to favour Mn(II) rather than Mn(III).

35 Examples of amino acids which have been found to be effective as uptake promoters in the compositions of the invention include all the native amino acids, i.e. alanine,

valine, leucine, tryptophan, methionine, isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, asparagine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lysine and histidine. Particularly 5 preferred as an uptake promoter in the composition of the invention are the amino acids L-aspartic acid and L-alanine.

The preferred vitamin is vitamin D<sub>3</sub>, but all subgroups of 10 vitamin D are suitable. Vitamin D is a fat soluble vitamin and soluble in organic solvents. A preferred solvent is polyethylene glycol.

The increase in the uptake of manganese for various uptake 15 promoters is demonstrated in the figures, which are MR images of the liver of rats after administering the contrast medium composition orally.

Using the compositions of the invention, the liver can be 20 effectively MR imaged with a significant reduction in the dosage of manganese otherwise required when administered orally.

The figures illustrate cross section images of the body of 25 rats in the liver region. The groups are defined in the example.

Figure 1 illustrates images from rats of group 2 (top), group 5 (mid left), group 1 (control) (mid right), and 30 group 7 (bottom).

The signal intensities were as follows:  
Group 2: Average signal intensity 112  
Group 5: Average signal intensity 134  
35 Group 1: Average signal intensity 98  
Group 7: Average signal intensity 121

Figure 2 illustrates images from rats of group 4 (top), group 3 (mid left), group 1 (control) (mid right), and group 7 (bottom).

5

The signal intensities were as follows:

Group 4: Average signal intensity 127

Group 3: Average signal intensity 139

Group 1: Average signal intensity 106

10 Group 7: Average signal intensity 129

Figure 3 illustrates images from rats of group 7 (top), group 4 (mid left), group 1 (control) (mid right), and group 2 (bottom).

15

The signal intensities were as follows:

Group 7: Average signal intensity 146

Group 4: Average signal intensity 135

Group 1: Average signal intensity 109

20 Group 2: Average signal intensity 101

In the composition according to the invention, the preferred molar ratio of manganese to uptake promoter is from 1:0,2 to 1:50, preferably 1:1 to 1:20, more preferably 25 1:3 to 1:6, and most preferably about 1:5.

If desired, the uptake promoter may be present in whole or in part as the counterion to the manganese ions.

30 The composition according to the invention may be used to achieve a so-called "double contrast effect" by increasing the signal level from the liver whilst at the same time decreasing that from the surrounding tissues, in particular from the gut. Such an effect enables yet further 35 enhancement of the image of the liver.

- In a particularly preferred embodiment, the composition of the invention may be used in combination with a second contrast agent having either a positive or negative contrast effect. Preferably, the compositions of the invention are used in combination with a second contrast agent having an opposing contrast effect. This results in a "double contrast effect" enabling visualisation and margin definition of the liver to be particularly enhanced.
- 10 As mentioned above, paramagnetic materials, such as manganese ions, may act as either positive or negative MRI contrast agents depending upon a number of factors, including the concentration of the ions at the imaging site and the magnetic field strength used in the imaging procedure. At the concentrations of manganese contemplated for use in the compositions of the invention, the manganese-containing contrast agent will in general function as a positive contrast agent. The second contrast agent is therefore conveniently negative contrast agent and may be any negative MRI contrast agent suitable for oral administration.

25 Examples of contrast agents for use in combination with the composition of the invention include iron (Fe), gadolinium (Gd) and dysprosium (Dy).

When using the composition of the invention to achieve a double contrast effect, it is particularly preferable to incorporate a viscosity enhancing agent which attains its 30 full viscosity enhancing effect only after administration of the contrast medium. The contrast medium is thus able to be ingested in a relatively tolerable form while yet developing the desired viscosity at or during passage towards the site which is to be imaged.

The compositions of the invention are particularly suited to use, if required, after dispersion in aqueous media, for imaging of the liver. For such a purpose the composition may be administered into the gastrointestinal tract orally,  
5 rectally or via a stomach tube.

Thus, viewed from a further aspect the present invention provides a method of generating a magnetic resonance image of a human or non-human, preferably mammalian, animal body,  
10 which method comprises administering into the gastrointestinal tract of said body an effective amount of a contrast medium comprising a physiologically acceptable manganese compound and a physiologically acceptable reducing compound containing a physiologically acceptable  
15 amino acid or a salt thereof, and/or vitamin D, and generating a magnetic resonance image of the liver and the gastrointestinal tract of said body.

In a further embodiment the invention provides a method of  
20 generating a magnetic resonance image of a human or non-human animal body, which method comprises administering into the gastrointestinal tract of said body an effective amount af a composition comprising: (a) a first contrast agent comprising a physiologically acceptable manganese compound and a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D, together with (b) a second  
25 contrast agent and generating a magnetic resonance image of the liver and abdomen of said body.

30 It is possible to formulate the contrast medium immediately or shortly prior to administration by mixing the uptake promoter with the manganese species. Thus, in a further aspect the invention also provides a MRI contrast agent kit  
35 comprising in a first container a physiologically acceptable manganese compound, and in a second container a

physiologically acceptable reducing compound containing an amino acid or a salt thereof, and/or vitamin D.

In a further embodiment of the invention the first  
5 container comprises a first contrast agent comprising a physiologically acceptable manganese compound together with a physiologically acceptable reducing compound containing an amino acid or a salt thereof, and/or vitamin D, and the second container comprises a second contrast agent.

10

The contrast agent composition of the invention may of course include components other than the uptake promoter, the manganese compound, for example conventional pharmaceutical formulation aids, such as wetting agents,  
15 buffers, disintegrants, binders, fillers, flavouring agents and liquid carrier media, such as sterile water, water/ethanol etc.

For oral administration, the pH of the composition is  
20 preferably in the acid range, e.g. 2 to 7, and while the uptake promoter may itself serve to yield a composition with this pH, buffers or pH adjusting agents may be used.

The contrast media may be formulated in conventional  
25 pharmaceutical administration forms, such as tablets, capsules, powders, solutions, dispersions, syrups, suppositories etc. When the contrast media can be administered orally, a patient can administer the contrast media himself 2 to 3 hours before being scanned. The  
30 patient is not obliged to stay in the hospital for several hours before being scanned.

The preferred dosage of the composition according to the present invention will vary according to a number of factors, such as the administration route, the age, weight  
35 and species of the subject, and the particular uptake

promoter used. Conveniently, the dosage of manganese will be in the range from 5 to 500  $\mu\text{mol}/\text{kg}$  body weight, preferably from 5 to 150  $\mu\text{mol}/\text{kg}$  body weight, more preferably from 10 to 100  $\mu\text{mol}/\text{kg}$  body weight, while the 5 dosage of the uptake promoter will be in the range from 5  $\mu\text{mol}$  to 1  $\text{mmol}/\text{kg}$  body weight, preferably from 25  $\mu\text{mol}$  to 0,5  $\text{mmol}/\text{kg}$  body weight.

10 The following example illustrates the effectiveness of the uptake of manganese for various uptake promoters.

The studies were carried out on seven groups of rats with six rats in each group. MRI examination was done with a quadrature knee-coil in a 0,1 T MRI unit. Each scanning 15 included four rats, and the examination was carried out three hours after the contrast medium was administered to the rats. If experiments are carried out with a higher tesla unit, e.g. 1,0 or 1,5 T, a larger increase in signal intensity can be expected.

20 After a 12 hour diet various contrast medium compositions were orally administered to the various groups of rats. The contrats medium was administered to the stomach of the rats via a catheter. Three hours after administration the rats 25 were killed and placed in a tube. Thereafter the rats were scanned.

30 The following non-limiting example illustrates various compositions administered to various groups of rats. The results of the scannings are illustrated in the figures.

In the example the units  $\mu\text{mol}/\text{kg}$  and  $\text{mg}/\text{kg}$  refer to  $\mu\text{mol}/\text{kg}$  body weight and  $\text{mg}/\text{kg}$  body weight

Example A

To group 1 (control) no contrast medium was administered.

5 To group 2 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate were administered

To group 3 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate and 300 µmol/kg (42 mg/kg) L-aspartic acid  
10 were administered.

To group 4 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate, 300 µmol/kg (42 mg/kg) L-aspartic acid and 0,1 mg/kg vitamin D<sub>3</sub>(10 µg/ml) were administered.

15

To group 5 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate and 300 µmol/kg (25 mg/kg) L-alanine were administered.

20 To group 6 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate, 300 µmol/kg (25 mg/kg) L-alanine and 0,1 mg/kg vitamin D<sub>3</sub>(10 µg/ml) were administered.

25 To group 7 100 µmol/kg (19,8 mg/kg) and 0,1 mg/kg vitamin D<sub>3</sub> (10 µg/ml) were administered.

Now referring to figur 1 it can be seen that the average signal intensity of the liver is substantially increased after administration orally of manganese(II)chloride tetrahydrate and L-alanine or manganese(II)chloride tetrahydrate and vitamin D<sub>3</sub>, respectively.

Referring to figur 2 it can be seen that the average signal intensity of the liver is substantially increased after 35 administration orally of manganese(II)chloride tetrahydrate

and L-aspartic acid and vitamin D<sub>3</sub>, L-aspartic acid or vitamin D<sub>3</sub>, respectively.

Referring to figur 3 it can be seen that the average signal intensity of the liver is substantially increased after administration of manganese(II)chloride tetrahydrate and vitamin D<sub>3</sub> or manganese(II)chloride tetrahydrate and L-aspartic acid and vitamin D<sub>3</sub>, respectively.

- 10 The following example illustrates preferred compositions administered to a human depending on the body weight.

Example B

15 Tabel

Body weight (kg)	Manganese(II) chloride tetrahydrate (g)	L-alanine (g)
60	1,188	1,500
70	1,386	1,750
80	1,568	2,000
90	1,782	2,250
100	1,980	2,500

Before being administered to the human the manganese(II) chloride tetrahydrate and L-alanine are dissolved in 250 ml of water.

## Claims

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1. A contrast medium composition comprising as an active  
5 ingredient a physiologically acceptable manganese compound  
and an uptake promoter, wherein the uptake promoter  
comprises a physiologically acceptable reducing compound  
containing a physiologically acceptable amino acid or a  
salt thereof, and/or vitamin D.
- 10 2. A composition as claimed in claim 1, wherein the uptake  
promoter comprises one or more of the compounds defined in  
claim 1.
- 15 3. A composition as claimed in claim 1 or claim 2, wherein  
the manganese compound is a salt, a chelate or another  
complex in which the manganese is present as Mn(II).
- 20 4. A composition as claimed in any one of the claims 1 to  
3, wherein the amino acid is an  $\alpha$ - or  $\beta$ -amino acid.
- 25 5. A composition as claimed in claim 4, wherein the amino  
acid is alanine, valine, leucine, tryptophan, methionine,  
isoleucine, proline, phenylalanine, serine, glycine,  
threonine, cysteine, asparagine, glutamine, tyrosine,  
aspartic acid, glutamic acid, arginine, lysine and  
histidine, preferably L-alanine or L-aspartic acid.
- 30 6. A composition as claimed in claim 4 or claim 5 further  
comprising vitamin D.
7. A composition as claimed in claim 6, wherein the vitamin  
is any subgroup of vitamin D, preferably vitamin D<sub>3</sub>.
- 35 8. A composition as claimed in any one of claims 1 to 3,  
wherein the uptake promoter is vitamin D.

9. A composition as claimed in claim 8, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D<sub>3</sub>
- 5 10. A composition as claimed in any of the preceding claims, wherein the uptake promoter is present in whole or in part as the counterion to the manganese ions.
- 10 11. A composition as claimed in any of the preceding claims further comprising a physiologically acceptable carrier or excipient.
- 15 12. A MRI contrast agent kit comprising in a first container a physiologically acceptable manganese compound, and in a second container a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D.
- 20 13. A contrast medium composition comprising as an active ingredient a manganese containing foodstuff, such as blueberry juice, green tea, and nuts, and an uptake promoter, wherein the uptake promoter comprises a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof and/or vitamin D.
- 25 14. A composition as claimed in claim 13, wherein the uptake promoter comprises one or more of the compounds defined in claim 13.
- 30 15. A composition as claimed in claim 13 or claim 14, wherein the manganese compound is a salt, a chelate or another complex in which the manganese is present as Mn(II).

16. A composition as claimed in any one of the claims 13 to 15, wherein the amino acid is an  $\alpha$ - or  $\beta$ -amino acid.
17. A composition as claimed in claim 16, wherein the acid is alanine, valine, leucine, tryptophan, methionine,  
5 isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, asparagine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lysine and histidine, preferably L-alanine or L-aspartic acid.
- 10 18. A composition as claimed in claim 16 or claim 17 further comprising vitamin D.
19. A composition as claimed in claim 18, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D<sub>3</sub>  
15 .
20. A composition as claimed in any one of claims 13 to 15, wherein the uptake promoter is vitamin D.
- 20 21. A composition as claimed in claim 20, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D<sub>3</sub>
- 25 22. A composition as claimed in any of the claims 13 to 21, wherein the uptake promoter is present in whole or in part  
as the counterion to the manganese ions.
- 30 23. A composition as claimed in any of the claims 13 to 22 further comprising a physiologically acceptable carrier or excipient.
- 35 24. A method of generating a magnetic resonance image of a human or non-human animal body, which method comprises administering into the gastrointestinal tract of said body a contrast medium comprising a physiologically acceptable manganese compound and a physiologically acceptable

reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D, and generating a magnetic resonance image of the liver and abdomen of said body.

5

25. A contrast medium composition comprising:

- a composition as claimed in any one of the claims 1 to 11 or 13 to 23, together with
- a second contrast agent.

10

26. A composition as claimed in claim 25, wherein the second contrast agent has an opposing contrast effect to said first contrast agent.

15

27. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent has a negative contrast effect.

20

28. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent has a positive contrast effect.

25

29. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent comprises a particulate ferromagnetic or superparamagnetic material.

30

30. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent comprises Fe, Gd or Dy ions bound to a polymeric matrix.

35

31. A method of generating a magnetic resonance image of a human or non-human body, which method comprises administering into the gastrointestinal tract of said body an effective amount of a composition as defined in claim 25 and generating a magnetic resonance image of the liver and abdomen of said body.

32. A MRI contrast agent kit comprising in a first container a first contrast agent comprising a physiologically acceptable manganese compound, a physiologically acceptable reducing compound containing a 5 physiologically acceptable amino acid or a salt thereof, and/or vitamin D, and in a second container a second contrast agent as defined in claim 29 or claim 30.

1/3

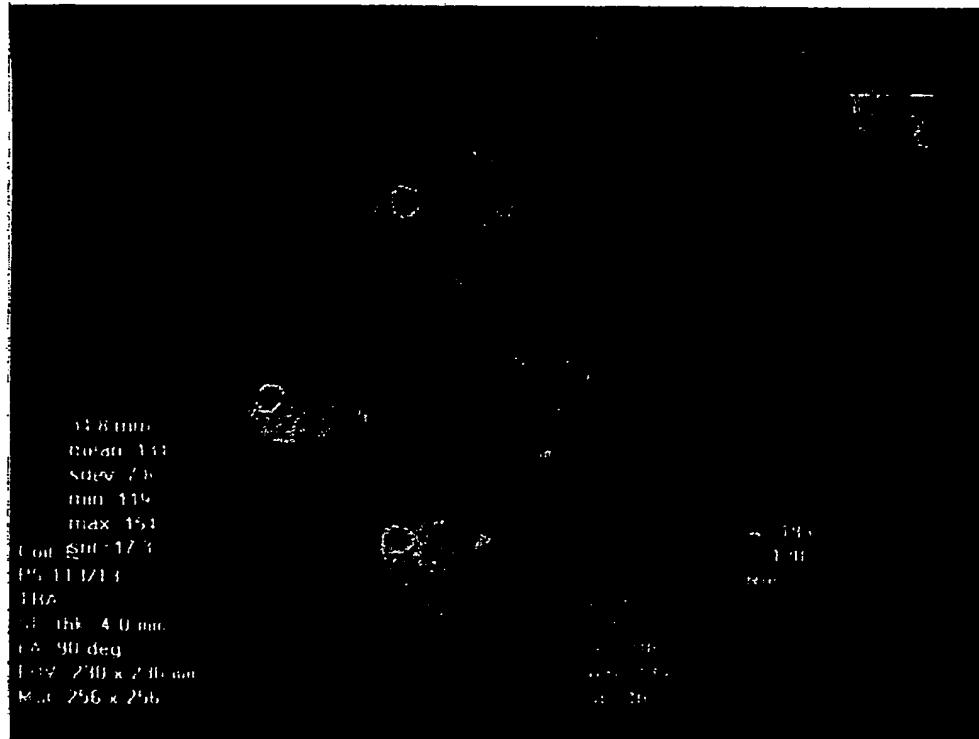
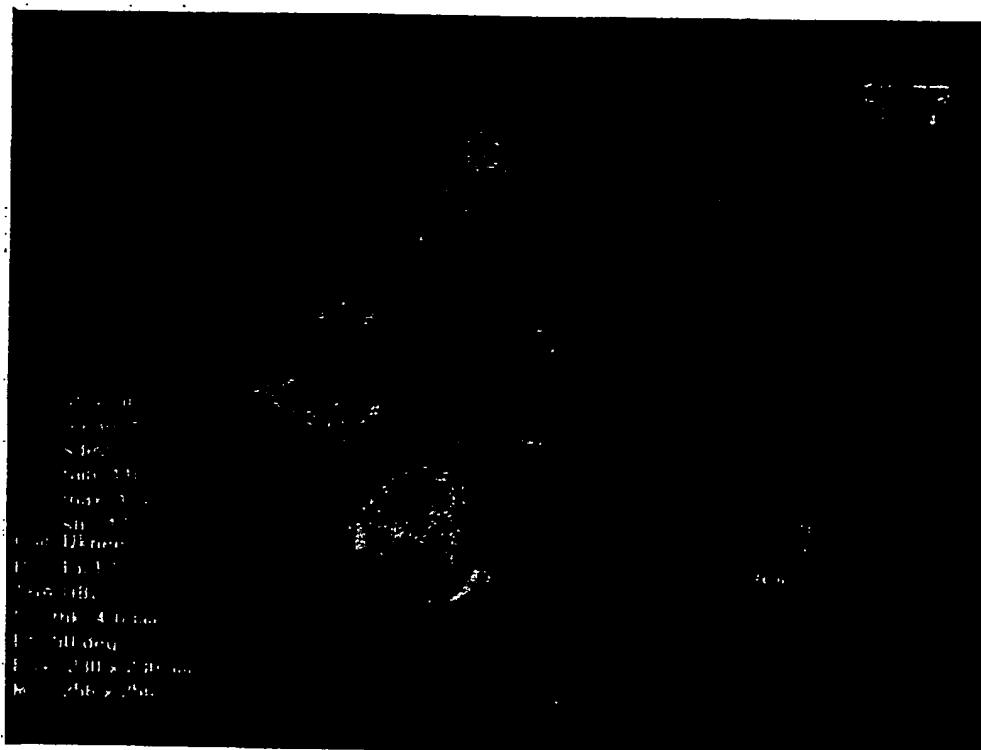


FIG. 1

2/3



**FIG. 2**

3/3

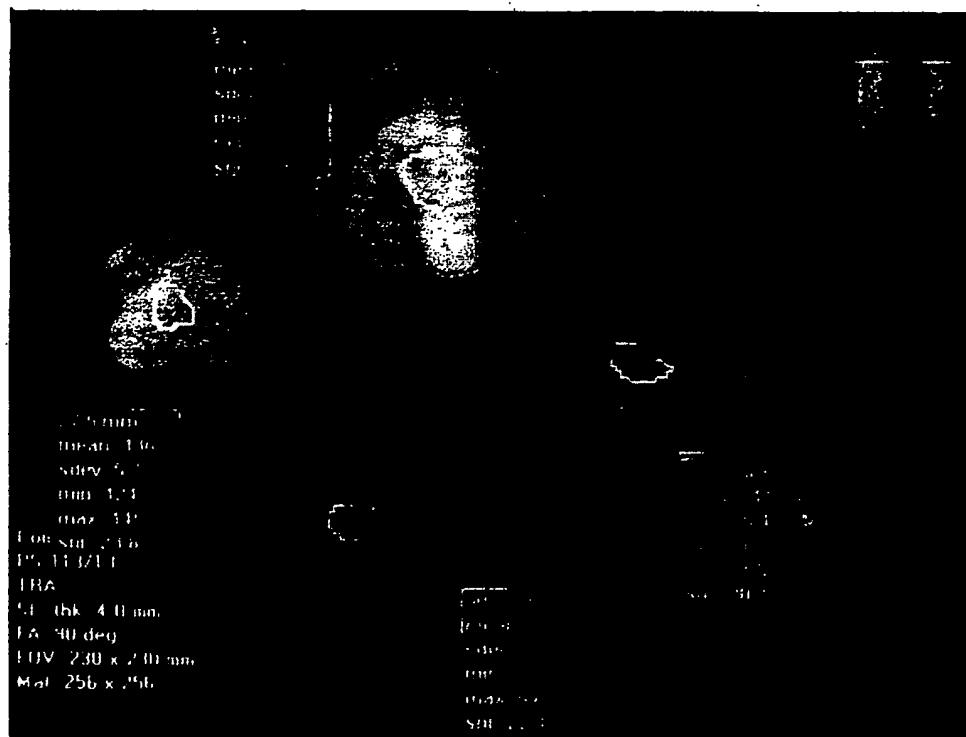


FIG. 3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00315

## A. CLASSIFICATION OF SUBJECT MATTER

### IPC6: A61K 49/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

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### IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9605867 A2 (NYCOMED IMAGING A/S), 29 February 1996 (29.02.96)  --	1-32
Y	EP 0308983 A2 (SALUTAR, INC.), 29 March 1989 (29.03.89), the claims  --	1-7,10-19, 22-24
Y	WO 9517910 A2 (BRACCO S.P.A. ET AL), 6 July 1995 (06.07.95), the claims  --	1-7,10-19, 22-24
Y	US 5292729 A (HARVEY H. ASHMEAD), 8 March 1994 (08.03.94), examples 12, 14, 15, the description, column 3, line 15-24  --	1-7,10-19, 22-24

Further documents are listed in the continuation of Box C.

See patent family annex.

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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 8704622 A1 (ALBION LABORATORIES, INC.),            13 August 1987 (13.08.87), page 7; page 15,            examples 13, 14, 28, the claims</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-----</p>	1-7,10-19, 22-24

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00315

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 24, 31

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 24, 31 are directed to a treatment/diagnosis of the human/animal body, the search has been carried out, based on the alleged effects of the compound/composition (Rule 39.1(iv)).

2.  Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Three different inventions were stated. For further information please see continuation sheet!

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.

- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00315

- 1 Claims 4-7, 16-19, and parts of claims 1-3, 10-15 and 22-24: a contrast medium composition, in which the contrast agent is containing a manganese compound, and as uptake promotor an amino acid, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.
- 2 Claims 8-9, 20-21, and parts of claims 1-3, 10-15 and 22-24: a contrast medium composition, in which the contrast agent is containing a manganese compound, and as uptake promotor vitamin D, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.
- 3 Claims 25-32: a contrast medium composition containing a manganese compound, an uptake promotor, together with a second contrast agent, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

The problem underlying the present application is, in its broadest form, the provision of safer contrast agents for NMR imaging, containing manganese ions.

As a solution to this problem, different uptake promotors are used.

The special technical feature, linking these solutions together, is the use of an uptake promotor for manganese ions.

This use is already known in the prior art. US,A, 5292729 and WO,A1, 87/04622 shows that the uptake of Mn in the G I-system are affected by amino acids.

Moreover NMR-compositions containing both manganese and amino acid promotors have been described before: see e.g. EP, A2, 0308983 and WO, A2, 95/17910.

For this reason, the special technical feature mentioned above can no longer be accepted as technical feature linking the different inventions together. Therefore, the present application lacks unity of invention.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

05/09/96

International application No.

PCT/DK 96/00315

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A2- 9605867	29/02/96	AU-A-	3262095	14/03/96
		GB-D-	9416767	00/00/00
		GB-D-	9416768	00/00/00
EP-A2- 0308983	29/03/89	AU-A-	2278988	06/04/89
		JP-A-	1259850	17/10/89
WO-A2- 9517910	06/07/95	IT-D-	MI932728	00/00/00
US-A- 5292729	08/03/94	AU-A-	4790193	15/03/94
		CA-A-	2142358	03/03/94
		EP-A-	0662830	19/07/95
		JP-T-	8502729	26/03/96
		WO-A-	9404141	03/03/94
WO-A1- 8704622	13/08/87	AU-B-	599637	26/07/90
		AU-A-	7038587	25/08/87
		CA-A-	1293444	24/12/91
		DE-A,T-	3787061	23/09/93
		EP-A,B-	0262178	06/04/88
		SE-T3-	0262178	
		JP-T-	63502749	13/10/88
		US-A-	4863898	05/09/89